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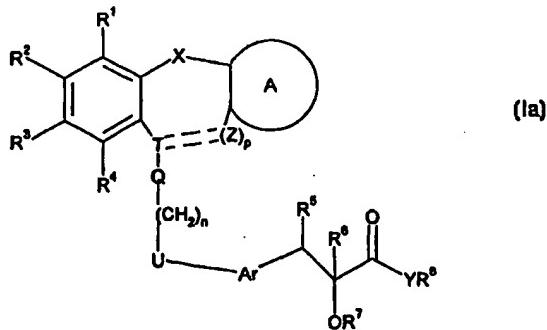
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(54) Title: NEW COMPOUNDS, THEIR PREPARATION AND USE



(57) Abstract

The present invention relates to compounds of general formula (Ia). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

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New Compounds, their Preparation and UseFIELD OF INVENTION

5 The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).
The present compounds reduce blood glucose and triglyceride levels and are accordingly
10 useful for the treatment of ailments and disorders such as diabetes and obesity.

The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, pharmaceutically acceptable solvates
15 and pharmaceutical compositions containing them.

The compounds are useful for the treatment and/or prophylaxis of insulin resistance (type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease and other cardiovascular disorders. The compounds of the present invention are also useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis. These compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and
25 treatment of bone loss, e.g. osteoporosis.

BACKGROUND OF THE INVENTION

30 Coronary artery disease (CAD) is the major cause of death in type 2 diabetic and metabolic syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious enough to be a single therapy of choice for the dyslipidaemia often observed in type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR α activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR γ acting primarily on adipose tissue.

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous differentiation process throughout life. Much evidence points to the central role of PPAR γ activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR γ to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR γ induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR α is involved in stimulating β -oxidation of fatty acids. In rodents, a PPAR α -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome

proliferation in rodents, PPAR α is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR α -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR α and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid b-oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. WO91/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

20 SUMMARY OF THE INVENTION

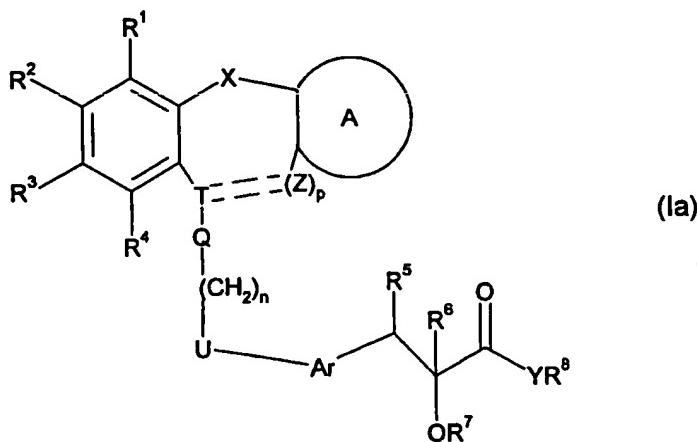
It seems more and more apparent that glucose lowering as a single approach does not overcome the macrovascular complications associated with type 2 diabetes and metabolic syndrome. Novel treatments of type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR α and PPAR γ activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (Ia):

5



- wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- or R¹ and R², R² and R³ and/or R³ and R⁴ may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C₁₋₆alkyl;

- ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy,

- hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- 10 X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C₁₋₁₂alkyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, halogen, C₁₋₆alkoxy, amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; T is >N-, >CH-, >C<, -CH₂-N<, Z is -CH₂- , =CH-, >N-, -O-, -S-, >CO, >SO, >SO₂, >NR¹⁵, wherein R¹⁵ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C₁₋₁₂alkyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹⁶, or -SO₂R¹⁷, wherein R¹⁶ and R¹⁷ independently of each other are selected from hydroxy, halogen, C₁₋₆alkoxy, amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; Q is -O-, -S-, >NR¹⁸, wherein R¹⁸ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C₁₋₁₂alkyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₁₂alkyl-

- amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹⁹, or -SO₂R²⁰, wherein R¹⁹ and R²⁰ independently of each other are selected from hydroxy, halogen, C₁₋₆alkoxy, amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl;
- U is -O-, -S-, >SO₂, >NR²¹, wherein R²¹ is hydrogen or C₁₋₆alkyl,
- T==(Z)_p represents a single bond or a double bond,
- Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C₁₋₆alkyl or aryl;
- R⁵ represents hydrogen, hydroxy, halogen, C₁₋₁₂alkoxy, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R⁵ forms a bond together with R⁶,
- R⁶ represents hydrogen, hydroxy, halogen, C₁₋₁₂alkoxy, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R⁶ forms a bond together with R⁵,
- R⁷ represents hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, C₁₋₁₂alkylaminocarbonyl, arylamino-carbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- R⁸ represents hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₁₂alkyl, aryl, hydroxyC₁₋₁₂alkyl or aralkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C₁₋₆alkyl;
- n is an integer ranging from 1 to 4,
- p is an integer ranging from 0 to 1,
- or a pharmaceutically acceptable salt thereof.

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In a preferred embodiment, the present invention is concerned with compounds of formula I wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, het-

eroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹²,
5 wherein R¹¹ and R¹² independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R¹ and R², R² and R³ and/or R³ and R⁴ may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C₁₋₆alkyl.

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In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, 15 heteroaralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

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- In another preferred embodiment, the present invention is concerned with compounds of
20 formula I wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, C₁₋₇alkyl-amino, arylamino, aralkylamino, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl or C₁₋₇alkylthio.
25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, hydroxyC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl or aralkoxyC₁₋₇alkyl.
30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen or C₁₋₇alkyl.
35 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R¹, R², R³, and R⁴ represent hydrogen.

- In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.
- 15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.
- 20
- 25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, C₁₋₇alkyl-amino, arylamino, aralkylamino, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl or C₁₋₇alkylthio.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl or C₁₋₇alkyl, C₄₋₇-

alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇-alkoxy, aryl, aralkyl, hydroxyC₁₋₇-alkyl, C₁₋₇-alkoxyC₁₋₇-alkyl, aryloxyC₁₋₇-alkyl or aralkoxyC₁₋₇-alkyl.

- In another preferred embodiment, the present invention is concerned with
5 compounds of formula I wherein ring A represents a 6 membered cyclic ring,
optionally substituted with one or more chlorine or methyl groups.

In another preferred embodiment, the present invention is concerned with
compounds of formula I wherein ring A represent a phenyl ring.

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- In another preferred embodiment, the present invention is concerned with
compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-,-
CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-,-(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-
CH₂-,-(C=O)-, -O-CH₂-O-, -(NR⁹)-S(O₂)-, -(NR⁹)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-
15 (SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)- or -CH₂-O-CH₂-, wherein R⁹ is hydrogen,
halogen, hydroxy, C₁₋₇alkyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl,
heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, hydroxyalkyl, amino,
acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₁₂alkyl,
aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₁₂alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino,
20 aryloxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

- In another preferred embodiment, the present invention is concerned with
compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-,-
CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-,-(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-
CH₂-,-(C=O)-, -O-CH₂-O-, -(NR⁹)-S(O₂)-, -(NR⁹)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-
25 (SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)- or -CH₂-O-CH₂-, wherein R⁹ is hydrogen,
halogen, hydroxy, C₁₋₇alkyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₇alkyl or
aralkoxyC₁₋₇alkyl.

- 30 In another preferred embodiment, the present invention is concerned with
compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-,-
CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-,-(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-
CH₂-,-(C=O)-, -O-CH₂-O-, -(NR⁹)-S(O₂)-, -(NR⁹)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-
(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)- or -CH₂-O-CH₂-, wherein R⁹ is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-,-CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-,-O-CH₂-O-, -(NR⁹)-, -S-, -(SO)- or -CH₂-O-CH₂-⁵, wherein R⁹ is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-,-CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂-,-O-CH₂-O-, -(NR⁹)-, -S- or -CH₂-¹⁰ O-CH₂-¹⁰, wherein R⁹ is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂-,-CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -O-CH₂-O- or -S-, wherein R⁹ is hydrogen.¹⁵

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >C<²⁰.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -CH₂-, =CH-, >N-, -O-, -S-, >CO, >SO, >SO₂.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is >N-.²⁵

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-, -S-, >NR¹⁸, wherein R¹⁸ is hydrogen or C₁₋₇alkyl.³⁰

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is >NR¹⁸, wherein R¹⁸ is hydrogen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein U is -O-.³⁵

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T==(Z), represents a double bond.

- 5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene optionally substituted with one or more C₁₋₆alkyl or aryl.

- 10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents phenyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₇alkoxy, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl or aralkyl, or R⁵ forms a bond together with R⁶.

- 15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen or R⁵ forms a bond together with R⁶.

-
- 20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₇alkoxy, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl or aralkyl, or R⁵ forms a bond together with R⁶.

- 25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ represents hydrogen or R⁵ forms a bond together with R⁶.

- 30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁷ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl, C₁₋₇alkoxycarbonyl, aryloxycarbonyl, C₁₋₇alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups.

- 35 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁷ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl or C₂₋₇-alkynyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁷ represents C₁₋₂alkyl.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl or aralkyl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ represents hydrogen or C₁₋₂alkyl.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₇alkyl, aryl, hydroxyC₁₋₇alkyl or aralkyl groups.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Y represents oxygen.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is an integer ranging from 2 to 3.

25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein p is 1.

30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A is benzo.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -O-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -S-.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -S- and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z is -CH₂- and p is 1.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is =CH- and p is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T==(Z), represents a single bond or a double bond.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >CH-.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is >C<.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -O-.

25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is -S-.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Q is >NR¹⁸, wherein R¹⁸ is H.

30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is 2.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein U is -O-.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar is phenylene.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁵ is H.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁶ is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁷ is ethyl.

15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R⁸ is H.

20 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein p is 0.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein A is a five membered ring containing S.

25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -(CHR⁹)-CH₂-, wherein R⁹ is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -O-(CHR⁹)-, wherein R⁹ is H.

30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -S-(CHR⁹)-, wherein R⁹ is H.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is -O-CH₂-O-.

Preferred compounds of the invention are:

5. 2-Ethoxy-3-[4-[2-(11H-5-oxa-10-thia-dibenzo[a,d]cyclohepten-11-yloxy)-ethoxy]-phenyl]-propionic acid,
3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-[4-[2-(Dibenzo[b,f][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl]-2-ethoxy-propionic acid,
10 3-[4-[2-(10,11-Dihydro-dibenzo[b,f]thiepin-10-ylsulfanyl)-ethoxy]-phenyl]-2-ethoxy-propionic acid,
3-(4-[2-[5H-Dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,
3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid
15 ethyl ester,
3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,
3-(4-[2-(6,11-Dihydrodibenzo[b,e]oxepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid
ethyl ester,
3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-
20 ethoxy-propionic acid ethyl ester,
3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-
ethoxy-propionic acid,
2-Ethoxy-3-(4-[2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethoxy]-
phenyl)-propionic acid ethyl ester,
25 3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-
ethoxy-propanoic acid ethyl ester,
3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-
ethoxy-propanoic acid,
3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-
30 ethoxypropanoic acid ethyl ester,
3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-
ethoxypropanoic acid;
or a pharmaceutically acceptable salt thereof.

Further, preferred compounds of the invention are:

2-Ethoxy-3-{4-[2-(11*H*-5-oxa-10-thia-dibenzo[*a,d*]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,

3-{4-[2-(Dibenzo[*b,f*][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

5 3-{4-[2-(10,11-Dihydro-dibenzo[*b,f*]thiepin-10-ylsulfanyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;

or a pharmaceutically acceptable salt thereof.

In the above structural formulas and throughout the present specification, the following terms

10 have the indicated meaning:

The terms "C₁₋₁₂-alkyl" as used herein, alone or in combination is intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration. represents e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like. Typical C₁₋₆-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

20 The terms "C_{2-n}-alkenyl" wherein n' can be from 3 through 15, as used herein, represents an olefinically unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl, and the like.

25 The terms "C_{2-n}-alkynyl" wherein n' can be from 3 through 15, as used herein, represent an unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl and the like.

30 The terms "C_{4-n}-alkenynyl" wherein n' can be from 5 through 15, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-hexadiene-5-yne and the like.

The term "C₁₋₁₂-alkoxy" as used herein, alone or in combination is intended to include those C₁₋₁₂-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The term "C₁₋₆-alkoxycarbonyloxy" is intended to include the above defined C₁₋₆-alkoxy groups attached to a carbonyloxy moiety, e.g. methoxycarbonyloxy, ethoxycarbonyloxy, etc..

As used herein the term "C₄₋₁₂-(cycloalkylalkyl)" represents a branched or straight alkyl group substituted at a carbon with a cycloalkyl group. Examples of such groups include, but are not limited to, cyclopropylethyl, cyclobutylmethyl, 2-(cyclohexyl)ethyl, cyclohexylmethyl, 3-(cyclopentyl)-1-propyl, and the like.

The term "C₁₋₁₂-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1-to-12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio. Example of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio.

The term "C₁₋₁₂alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C₁₋₁₂-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino. Example of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino and cyclohexylamino.

The term "hydroxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl etc..

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenylamino, naphthylamino, etc..

- 5 The term "aralkylamino" as used herein, alone or in combination, refers to an aralkyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-(1-naphtyl)ethylamino and the like.
- 10 The term "aminoC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached an amino group, e.g. aminoethyl, 1-aminopropyl, 2-aminopropyl etc..

- 15 The term "aryloxycarbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. phenoxy carbonyl, 1-naphthyoxy carbonyl or 2-naphthyoxy carbonyl, etc..

-
- 20 The term "aralkoxycarbonyl" as used herein, alone or in combination, refers to an aralkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphtyl)ethoxycarbonyl, etc..

- 25 The term "C₁₋₁₂alkoxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached a C₁₋₁₂alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl, etc..

- 30 The term "aryloxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g. phenoxy methyl, phenoxydodecyl, 1-naphthyoxyethyl, 2-naphthyoxypropyl, etc..
- 35 The term "aralkoxyC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached an aralkoxy as defined herein, e.g. benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphtyl)ethoxymethyl, etc..

The term "thioC₁₋₁₂alkyl" as used herein, alone or in combination, refers to a C₁₋₁₂alkyl as defined herein whereto is attached a group of formula -SR''' wherein R''' is hydrogen, C₁₋₆alkyl or aryl, e.g. thiomethyl, methylthiomethyl, phenylthioethyl, etc..

5

The term "C₁₋₁₂alkoxycarbonylamino" as used herein, alone or in combination, refers to a C₁₋₁₂alkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. methoxycarbonylamino, carbethoxymino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino, etc..

10

The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an aryloxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenoxy carbonylamino, 1-naphthyoxy carbonylamino or 2-naphthyoxy carbonylamino, etc..

15

The term "aralkoxycarbonylamino" as used herein, alone or in combination, refers to an aralkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzyloxycarbonylamino, phenethoxycarbonylamino, 3-phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-

20 naphtyl)ethoxycarbonylamino, etc..

The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenyl, naphthyl, (1-naphtyl or 2-naphtyl) optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy.

25

The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenylene, naphthylene, optionally substituted with halogen, amino, hydroxy, C₁₋₆-alkyl or C₁₋₆-alkoxy.

30 The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

The term "C₁₋₆-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino, and the like.

5 The term "acyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl, and the like.

10 The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. acyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy, and the like.

15 The term "C₁₋₁₂-alkoxycarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₁₂-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

20 The term "a cyclic ring containing from 5 to 7 carbon atoms" as used herein refers to a monocyclic saturated or unsaturated or aromatic system, wherein the ring may be cyclopentyl, cyclopentenyl, cyclohexyl, phenyl or cycloheptyl.

25 The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl and 9-bicyclo[3.3.1]nonanyl.

30 The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole,

quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen.

The term "aralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthoxy or 2-naphthoxy.

The term "aralkoxy" as used herein refers to a C₁₋₆-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

The term "heteroaralkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

The term "heteroaralkoxy" as used herein refers to a heteroaralkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl,

(3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen.

- The term "C₁₋₆-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl and 2,2-dimethylpropylsulfonyl.
- 5 The term "C₁₋₆-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-10 hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl and 2,2-dimethylpropylaminosulfonyl.
- 15

The term "C₁₋₆-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a sulfonyl group such as 20 dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl, and the like.

The term "C₁₋₆-alkylsulfinyl" as used herein refers to a monovalent substituent comprising a straight or branched C₁₋₆-alkyl group linked through a sulfinyl group (-S(=O)-); such as e.g. methylsulfinyl, ethylsulfinyl, isopropylsulfinyl, butylsulfinyl, pentylsulfinyl, and the like.

The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino, and the like.

The term "(C₃₋₆-cycloalkyl)C₁₋₆-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C₃₋₆-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubsti-

- tuted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl, and the like.
- 5 The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; e.g. phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio, and the like.
- 10 The term "arylsulfinyl" as used herein refers to an aryl group linked through a sulfinyl group (-S(=O)-), the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfinyl, (4-chlorophenyl)sulfinyl, and the like.
- The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C₁₋₆-alkyl, halogen, hydroxy or C₁₋₆-alkoxy; such as e.g. phenylsulfonyl, tosyl, and the like.
- 15 The term "C₁₋₆-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl and 2-2-dimethylpropylaminocarbonyl.
- 20 The term "C₁₋₆-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C₁₋₆-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl, and the like.
- 25 The term "C₁₋₆-monoalkylaminocarbonylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with a C₁₋₆-monoalkylaminocarbonyl group, e.g. methylaminocarbonylamino, ethylamino-carbonylamino, n-propylaminocarbonylamino, isopropylaminocarbonylamino, n-butylaminocarbonylamino, sec-butylaminocarbonylamino,
- 30

isobutylaminocarbonylamino, tert-butylaminocarbonylamino, and 2-methylbutylaminocarbonylamino.

- The term "C₁₋₆-dialkylaminocarbonylamino" as used herein refers to an amino group wherein
5 one of the hydrogen atoms is substituted with a C₁₋₆-dialkylaminocarbonyl group, such as di-methylaminocarbonylamino, N-ethyl-N-methylaminocarbonylamino, diethylaminocarbony-lamino, dipropylaminocarbonylamino, N-(n-butyl)-N-methylaminocarbonylamino, di(n-pentyl)aminocarbonylamino, and the like.
- 10 As used herein, the phrase "heterocycl" means a monovalent saturated or unsaturated group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocycl" includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline); 5-membered heterocycles having two heteroatoms in 1,2 or
15 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine,
20 morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles
25 with one heteroatom (e.g. piperidine); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes, but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, 5 imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 10 1,4-dioxolanyl, 5-membered heterocycles having one hetero atom (e.g. thiophenes, pyrroles, furans); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines); 5-membered heterocycles having three heteroatoms (e.g. triazoles, thiadiazoles); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, 15 quinazolines, morpholines); 6-membered heterocycles with three heteroatoms (e.g. 1,3,5-triazine); and 6-membered heterocycles with four heteroatoms.

As used herein, the phrase "5- or 6-membered nitrogen containing ring" refers to a

monovalent substituent comprising a monocyclic-unsaturated-or-saturated-or-aromatic

20 system containing one or more carbon, nitrogen, oxygen or sulfur atoms or a combination thereof and having 5 or 6 members, e.g. pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl and 1,4-dioxolanyl.

25

Certain of the above defined terms may occur more than once in the above formula (Ia), and upon such occurrence each term shall be defined independently of the other.

Pharmaceutically acceptable salts forming part of this invention include salts of the carboxylic acid moiety such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succi-

nates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprising other solvents of crystallization such as alcohols.

5

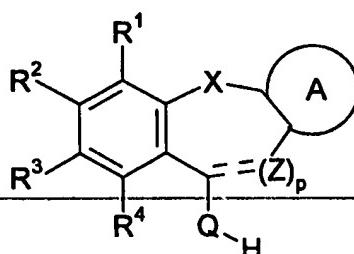
The pharmaceutically acceptable salts are prepared by reacting the compound of formula (Ia) with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guandine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (Ia) may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (Ia) may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula (Ia) forming part of this invention may be prepared by crystallization of compound of formula (Ia) under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

- 5 10 The invention also relate to methods of preparing the above mentioned compounds, comprising:

a) reacting a compound of formula II

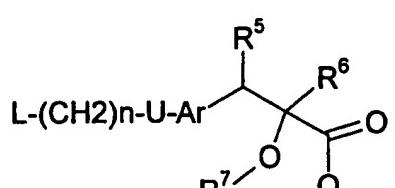


15

II

wherein R¹-R⁴, A, X, Z, p and Q are defined as above, with a compound of formula III

20



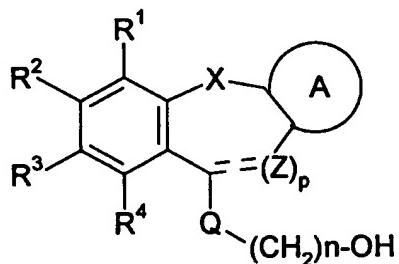
III

25

wherein L is a leaving group such as halogen, p-toluenesulfonate, methanesulfonate and the like and wherein n, U, Ar, R⁵-R⁸ are defined as above except that R⁸ is not H, to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁸, A, X, Z, U and Q are defined as above except that R⁸ is not H.

5

b) reacting a compound of formula IV

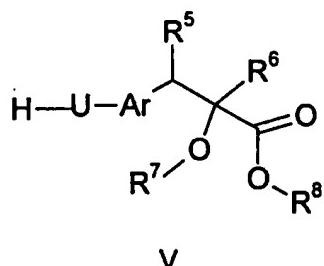


10

IV

wherein R¹-R⁴, A, X, Z, Q, p and n are defined as above, with a compound of formula V

15

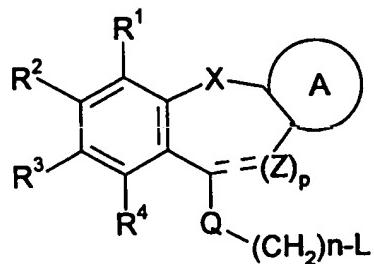


V

20 wherein U, Ar and R⁵-R⁸ are defined as above except that R⁸ is not H, by using suitable coupling agents such as dicyclohexyl urea, triarylphosphine/ dialkylazadicarboxylate such as PPh₃/ DEAD (Diethylazodicarboxylate) and the like, to obtain a compound of formula I, wherein n, p, Ar, R¹-R⁸, A, X, Z, U

and Q are defined as above except that R⁸ is not H, and U is not C.

c) reacting a compound of formula VI

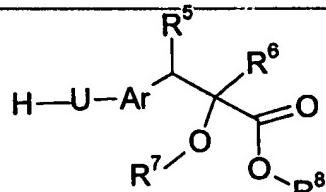


5

VI

wherein L is a leaving group such as halogen, p-toluenesulfonate, methanesulfonate and the like and wherein R¹-R⁴, A, X, Z, Q, p and n are defined as above, with an compound of formula V

10



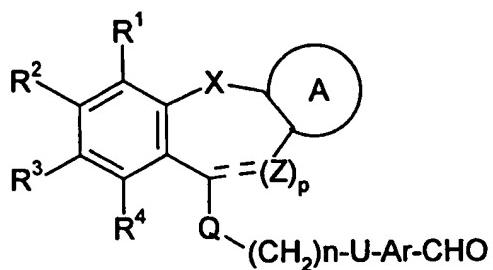
V

15 wherein U, Ar and R⁵-R⁸ are defined as above except that R⁸ is not H, to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁸, A, X, Z, U and Q are defined as above except that R⁸ is not H and U is not C.

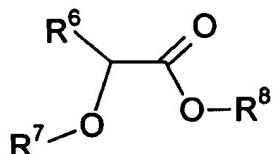
d) reacting a compound of formula VII

20

30



5 wherein R¹-R⁴, A, X, Z, Q, U, Ar, p, and n are defined as above, with an compound of formula VIII

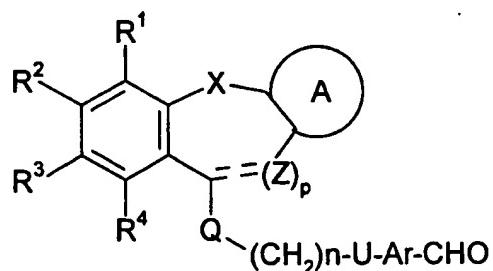


10

wherein R⁶-R⁸ are defined as above except that R⁸ is not H, to obtain the β -hydroxy aldo product, which may be dehydroxylated or dehydrated to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁸, A, X, Z, U and Q are defined as above except that R⁸ is not H.

15

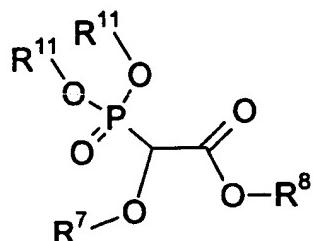
e) reacting a compound of formula VII



20

wherein R¹-R⁴, A, X, Q, Z, U, Ar, p and n are defined as above, with an compound of formula IX

5

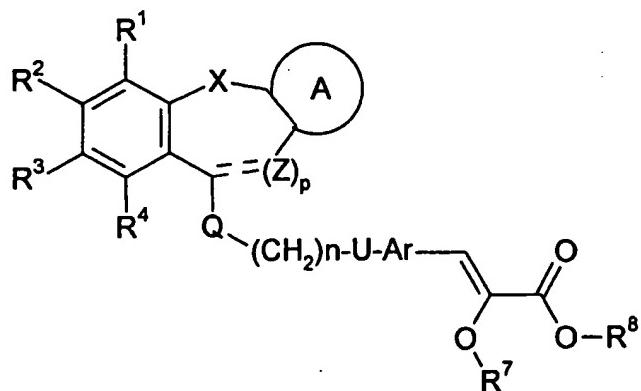


IX

- 10 wherein R⁷ and R⁸ are defined as above except that R⁸ is not H, and wherein R¹¹ is a lower alkyl group to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁴, R⁷-R⁸, A, X, Z, U and Q are defined as above except that R⁸ is not H and wherein R⁵ forms a bond together with R⁶.

15

f) hydrogenation of a compound of formula X

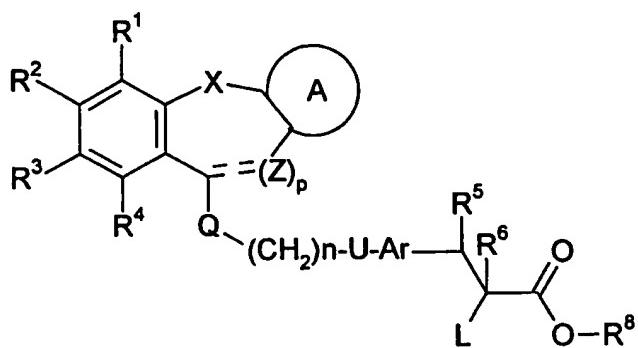


X

wherein n, p, Ar, R¹-R⁴, R⁷-R⁸, A, X, Z, U and Q are defined as above except that R⁸ is not H, to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁴, R⁷-R⁸, A, X, Z, U and Q are defined as above except that R⁸ is not H and wherein R⁵ and R⁶ is hydrogen.

5

g) reacting a compound of formula XI



10

XI

wherein L is a leaving group such as halogen and R¹-R⁸, A, X, Q, Z, U, p and n are defined as above except that R⁸ is not H, with an alcohol of formula XII

15

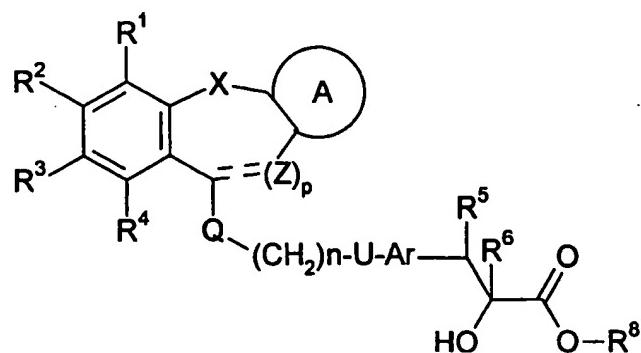


XII

wherein R⁷ is defined as above, to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁸, R⁷, A, X, Z, U and Q is defined as above except that R⁸ is not H.

20

h) reacting a compound of formula XIII



XIII

wherein n, p, Ar, R¹-R⁶, A, X, Z, U and Q is defined as above and wherein R⁸ is defined as
 5 above except that R⁸ is not H, with a compound of formula XIV

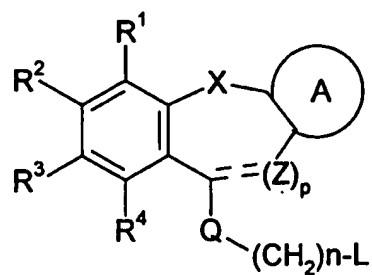


XIV

10

wherein R⁷ is defined as above and wherein "Hal" represents Cl, Br, or I to obtain a com-
 pound of formula (Ia) wherein n, p, Ar, R¹- R⁸, A, X , Z, U and Q is defined as above except
 that R⁸ is not H.

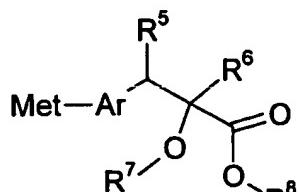
15 i) reacting a compound of formula VI



VI

wherein L is a leaving group such as halogen, p-toluenesulfonate, methanesulfonate and the like and wherein R¹-R⁴, A, X, Q, Z, p and n are defined as above, with a nucleophilic compound of formula XV

5

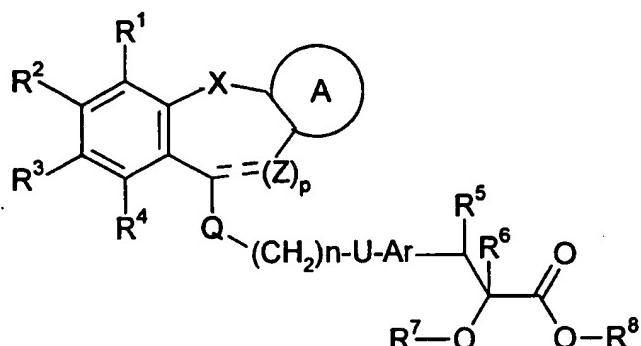


XV

wherein "Met" is a metal such as zinc or copper, carrying suitable ligands chosen preferentially from trifluoro-methanesulfonate, halide or C₁-C₆ alkyl, to obtain a compound of formula (Ia) wherein n, p, Ar, R¹-R⁸, R⁷, A, X and Q is defined as above except that R⁸ is not H, and U is C.

15

j) saponification a compound of formula XVI



XVI

20

wherein n, p, Ar, R¹-R⁸, A, X, Z, U and Q is defined as above except that R⁸ is not H, to obtain a compound of formula (Ia) wherein n, Ar, R¹-R⁷, A, X, Z and Q is defined as above and wherein R⁸ is H.

The starting materials are commercially available or readily prepared by methods familiar to those skilled in the art.

5

PHARMACOLOGICAL METHODS

In vitro PPAR alpha and PPAR gamma activation activity.

10 Principle

The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from
15 the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid
20 contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The
25 amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

Methods

30 Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluence of 80 % at transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR α and γ was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPAR α : aa 167 - C-term; PPAR γ : aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1 α LBD and pM1 γ LBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

10

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 μ l growth medium including de-lipidated serum) for 24 h followed by luciferase assay.

15

Luciferase assay: Medium including test compound was aspirated and 100 μ l PBS incl. 1mM Mg $^{++}$ and Ca $^{++}$ was added to each well. The luciferase assay was performed using the Luciferase kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting SPC mode on a Packard Instruments top-counter.

20

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula (Ia) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula (Ia) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which

may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used.

For example, the active compound will usually be mixed with a carrier, or diluted by a carrier,

5 or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols,

10 polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include

15 any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed-release-of-the-active-ingredient-after-administration-to-the-patient-by

20 employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

25 The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

30 If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin

capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

- For nasal administration, the preparation may contain a compound of formula (Ia) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.
- 5
- 10 For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

15

A typical tablet which may be prepared by conventional tabletting techniques may contain:

| | | |
|----|--|--------|
| 20 | Core: | |
| | Active compound (as free compound or salt thereof) | 5 mg |
| | Colloidal silicon dioxide (Aerosil) | 1.5 mg |
| | Cellulose, microcryst. (Avicel) | 70 mg |
| | Modified cellulose gum (Ac-Di-Sol) | 7.5 mg |
| 25 | Magnesium stearate | Ad. |

Coating:

| | |
|--------------------------|--------|
| HPMC approx. | 9 mg |
| *Mywacett 9-40 T approx. | 0.9 mg |

30

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

- Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

- The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to 10 about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and 15 the preference and experience of the physician or veterinarian in charge.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

- 20 Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula (Ia) admixed with a pharmaceutically acceptable carrier or diluent.

- 25 In a further aspect, the present invention relates to a method of treating and/or preventing type I or type II diabetes.

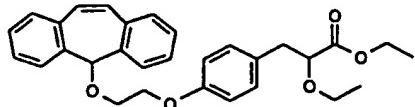
- In a still further aspect, the present invention relates to the use of one or more compounds of the general formula (Ia) or pharmaceutically acceptable salts thereof for the preparation of a 30 medicament for the treatment and/or prevention of type I or type II diabetes.

Any novel feature or combination of features described herein is considered essential to this invention.

The invention will now be described in further detail with reference to the following examples. The examples are provided for illustrative purposes, and are not to be construed as limiting the scope of the invention in any way.

5

EXAMPLE 1



10

3-(4-[2-[5H-Dibenzo[a,d]cyclohepten-5-yloxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

15 a)

Dibenzosuberenol (2.08 g, 10 mmol) was dissolved in dry THF (20 mL) at 0 °C. Sodium hydride (1.0 g of 50 % mineral oil dispersion, 20 mmol) was added. After 10 min. *tert*-butylbromoacetate (4.0 g, 20.0 mmol) was added over a period of 20 min and then stirred for 1 h. The reaction mixture was quenched with water at 0 °C and the product extracted with ethyl acetate. The combined extracts were dried (MgSO_4), and concentrated in vacuo. The product was redissolved in ether (20 mL) and added dropwise to an ether (15 mL) suspension of lithium aluminium hydride (190 mg, 5.0 mmol). The reaction was stirred 16 h at room temperature, quenched with water. The ether solution was washed with water, dried, and concentrated in vacuo to give 1.3 g (50%) of 2-(5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethanol.

20

25 b)

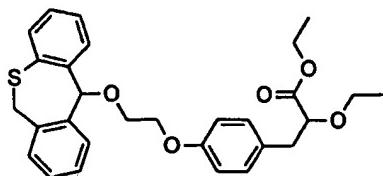
Under a nitrogen atmosphere, 2-(5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethanol (400 mg, 1.6 mmol), tributylphosphine (480 mg, 2.4 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380 mg, 1.6 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (480 mg, 2.4 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and

30

the stirring was continued for 2h. The mixture was added water and the product extracted with ethyl acetate. The combined organic phases was dried (MgSO_4), and concentrated in vacuo. The residue was purified chromatography eluting with ethyl acetate/hexane (1:9) to give 350 mg (47%) of the title compound: MS 472 (M^+).

5

EXAMPLE 2



10

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

a)

15 6,11-Dihydrodibenzo[b,e]thiepin-11-ol (1.14 g, 5 mmol) was dissolved in dry THF (25 mL) at 0 °C. Sodium hydride (0.24 g of 50 % mineral oil dispersion, 5 mmol) was added portionwise at 0 °C and then refluxed for 30 min. *tert*-Butylbromoacetate (980 mg, 5.0 mmol) in dry THF (10 mL) was added over a period of 20 min followed by a 30 min reflux. The reaction mixture was quenched with water at 0 °C and the product extracted with ether. The combined extracts were dried (MgSO_4), and concentrated in vacuo. The product was redissolved in ether and added dropwise to an ether (15 mL) suspension of lithium aluminium hydride (190 mg, 5.0 mmol). The reaction was stirred 16 h at room temperature, quenched with water, cooled, and filtered through Decalit. The ether solution was washed with saturated NaCl, dried, and purified by chromatography eluting with ethyl acetate/dichloromethan (1:10) to give 850 mg (63%) of 2-(6,11-dihydrodibenzo[b,e]thiepin-11-yloxy)-ethanol. ^1H NMR (300 MHz, CDCl_3) δ 3.55-3.70 (m, 2H), 3.75-3.85 (m, 2H), 4.00 (bs, 1H), 4.85 (bs, 1H), 5.55 (bs, 1H), 7.03-7.13 (m, 3H), 7.13-7.48 (m, 5H).

b)

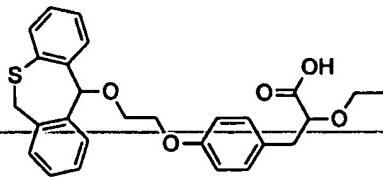
30 Under a nitrogen atmosphere, 2-(6,11-dihydrodibenzo[b,e]thiepin-11-yloxy)-ethanol (340 mg, 1.25 mmol), tributylphosphine (280 mg, 1.37 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-

propionic acid ethyl ester (330 mg, 1.37 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (350 mg, 1.37 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. Heptane (10 mL) was added to the reaction mixture and dihydro-ADDP separated out was filtered off. After evaporation of the solvent the product was purified chromatography eluting with ethyl acetate/heptane (1:4) to give 460 mg (75%) of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 1.15 (t, 3H), 1.25 (t, 3H), 2.95 (d, 2H), 3.30-3.40 (m, 1H), 3.55-3.65 (m, 1H), 2.85 (t, 2H), 3.95 (t, 1H), 4.10-4.22 (m, 4H), 4.5-5.1 (bs, 1H), 5.60-5.75 (bs, 1H), 6.82 (d, 2H), 7.05-7.50 (m, 10H).

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EXAMPLE 3

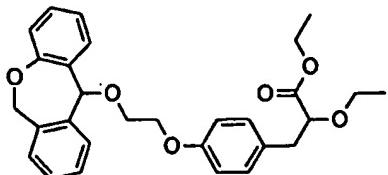
15

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid

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3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester (example 2) (220 mg, 0.44 mmol) in ethanol (5 mL) was added NaOH 1N (0.9 mL, 0.9 mmol). The mixture was stirred at room temperature for 16 h. The ethanol was evaporated of and pH adjusted with HCl 1N to pH 1. After extraction with dichloromethane the product was purified by chromatography, using dichloromethane/methanol (9:1) as eluent, to give 126 mg (62%) of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 1.15 (t, 3H), 2.85-3.10 (m, 2H), 3.32-3.42 (m, 1H), 3.52-3.65 (m, 1H), 2.85 (t, 2H), 3.95-4.05 (m, 1H), 4.10-4.22 (m, 2H), 4.5-5.1 (bs, 1H), 5.60-5.75 (bs, 1H), 6.82 (d, 2H), 7.05-7.50 (m, 10H).

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EXAMPLE 4

- 5 3-(4-[2-(6,11-Dihydrodibenzo[b,e]oxepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid
ethyl ester
-

a)

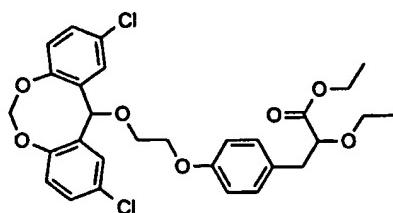
10 6,11-Dihydrodibenzo[b,e]oxepin-11-ol (1.06 g, 5 mmol) was dissolved in dry THF (25 mL) at 0 °C. Sodium hydride (0.24 g of 50 % mineral oil dispersion, 5 mmol) was added portion-wise at 0 °C and then refluxed for 30 min. *tert*-Butylbromoacetate (980 mg, 5.0 mmol) in dry THF (10 mL) was added over a period of 20 and the mixture stirred at 35 °C for 16h. The reaction mixture was quenched with water at 0 °C and the product extracted with ether. The combined extracts were dried (MgSO_4), and concentrated in vacuo. The product was redissolved in ether and added dropwise to an ether (15 mL) suspension of lithium aluminium hydride (190 mg, 5.0 mmol). The reaction was stirred 48 h at room temperature, quenched with water, cooled, and filtered through Decalit. The ether solution was washed with saturated NaCl, dried, and purified by chromatography eluting with ethyl acetate/dichloromethan (1:10) to give 267 mg (21%) of 2-(6,11-dihydrodibenzo[b,e]oxepin-11-yloxy)-ethanol.

b)

Under a nitrogen atmosphere, 2-(6,11-dihydrodibenzo[b,e]oxepin-11-yloxy)-ethanol (256 mg, 1.0 mmol), tributylphosphine (223 mg, 1.1 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (262 mg, 1.1 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (278 mg, 1.1 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 16 h. Heptane (10 mL) was added to the reaction mixture and dihydro-ADDP separated out was filtered off. After evaporation of the solvent the product was purified chromatography eluting with ethyl acetate/heptane (1:4) to give 175 mg (37%) of the title compound: ^1H NMR (300 MHz, CDCl_3) δ 1.15 (t, 3H), 1.25 (t, 3H), 2.93

(d, 2H), 3.30-3.40 (m, 1H), 3.55-3.65 (m, 1H), 3.65-3.75 (m, 1H), 3.78-3.88 (m, 1H), 3.95 (t, 1H), 4.10 (t, 2H), 4.15 (q, 2H), 4.85 (d, 1H), 5.25 (s, 1H), 6.15 (d, 1H), 6.75 (d, 2H), 6.85-6.95 (m, 2H), 7.10 (d, 2H), 7.15-7.40 (m, 6H).

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EXAMPLE 5

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3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

a)

15 To a solution of bis-(5-chloro-2-hydroxyphenyl)-methane (24.4 g, 90.7 mmol) in dry DMF (340 mL) was added diiodomethane (25.5 g, 95.0 mmol) and potassium carbonate (18.2 g, 132 mmol). The mixture was stirred at 105 °C for 16 h. The mixture was added to ice water (1200 mL) and stirred for 30 min. The product was isolated by filtration, and washed with water and suspended in a mixture of ethanol (200 mL) and 4N NaOH (50 mL). The mixture
20 was heated at 80 °C for 1 h. The mixture was added to water (600 mL) and 21.45 g (84%) 2,10-dichloro-12H-dibenzo[d,g][1,3]-dioxocin was isolated by filtration.

b)

To a solution of 2,10-dichloro-12H-dibenzo[d,g][1,3]-dioxocin (21.4 g, 76.1 mmol) and N-bromosuccinimide (13.5 g, 76.1 mmol) in tetrachloromethane (275 mL) was added azobisisobutyronitrile (200 mg, 1.2 mmol). The mixture was heated at 80 °C for 24 h. Another 3 x azobisisobutyronitrile (200 mg, 1.2 mmol) was added within the 24 h. The mixture was filtrated and the solution phase concentrated in vacuo. The residue was added dichloromethane (30 mL) and ether (100 mL). The mixture was filtered and the solution phase
30 concentrated in vacuo. The residue was submitted to flash chromatography eluting with

heptane/ethyl acetate (3:1) to give 7.4 g (27%) of 12-bromo-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene.

c)

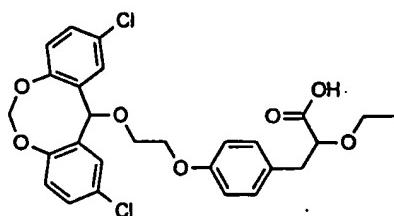
- 5 A mixture of 12-bromo-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene (900 mg, 2.5 mmol), 2-bromoethanol (3.75 g, 30 mmol) and potassium carbonate (1.0 g, 7.2 mmol) in dichloromethane (10 mL) was heated at 120 °C for 4 h. The reaction mixture was concentrated in vacuo, added water (25 mL) and the product extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried (MgSO_4), filtered and evaporated to give 832 mg (82%) of 12-(2-bromo-ethoxy)-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene.

d)

- To a solution of 12-(2-bromo-ethoxy)-2,10-dichloro-12H-5,7-dioxa-dibenzo[a,d]cyclooctene (404 mg, 1.0 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (238 mg, 1.0 mmol) in dry toluene (6 mL) was added potassium carbonate (276 mg, 2.0 mmol) and 18-crown-6 (528 mg, 2.0 mmol). The mixture was heated at 60 °C for 16 h. The mixture was filtered, and concentrated in vacuo. The residue was submitted to flash chromatography using toluene/ethyl acetate (19:1) as eluent to give 297 mg (53%) of the title compound; ^1H NMR (300 MHz, CDCl_3) δ 1.18 (t, 3H), 1.25 (t, 3H), 2.96 (d, 2H), 3.30-3.42 (m, 1H), 3.55-3.65 (m, 1H), 3.90-3.95 (m, 2H), 4.0 (t, 1H), 4.15-4.25 (m, 4H), 4.55 (d, 1H), 5.87 (d, 1H), 6.18 (s, 1H), 6.88-6.95 (m, 4H), 7.10-7.25 (m, 4H), 7.60 (d, 2H).

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EXAMPLE 6



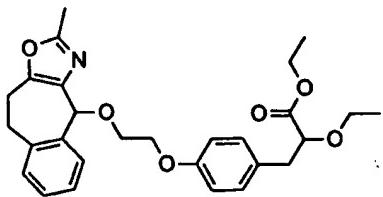
- 30 3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy]-ethoxy]-phenyl)-2-ethoxy-propionic acid

3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester (example 5) (450 mg, 0.8 mmol) in ethanol (8 mL) was added NaOH 1N (4.0 mL, 4.0 mmol). The mixture was stirred at room temperature for 16 h.

- 5 The sodium salt of the title compound was isolated by filtration and washed with ethanol/water to give 272 mg (61%): m.p. 240-241°C. ¹H NMR (300 MHz, DMSO-d₆) δ 0.95 (t, 3H), 2.55-2.65 (m, 1H), 2.80-2.88 (m, 1H), 3.05-3.15 (m, 1H), 3.48-3.60 (m, 2H), 3.80-3.90 (m, 2H), 4.15-4.25 (m, 2H), 4.65 (d, 1H), 5.90 (d, 1H), 6.13 (s, 1H), 6.85 (d, 2H), 7.05 (d, 2H), 7.15 (d, 2H), 7.23-7.30 (m, 2H), 7.55-7.58 (m, 2H).

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EXAMPLE 7



15

2-Ethoxy-3-(4-[2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethoxy]-phenyl)-propionic acid ethyl ester

a)

To a ice cooled solution of oxazol (1.08 g, 5.0 mmol) in dry THF (50 mL) was added sodium hydride (500 mg of 60 % mineral oil dispersion, 10 mmol). After stirring for 20 min. *tert*-butyl bromoacetate (1.95 g, 10 mmol) was added. Stirring at room temperature for 1 h. The reaction mixture was quenched with water and the product extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo to give 1.47 g (90%) of (2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-acetic acid *tert*-butyl ester.

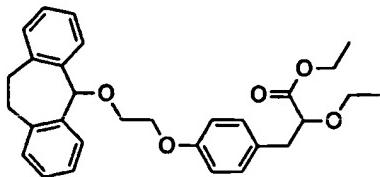
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b)

To a solution of (2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-acetic acid *tert*-butyl ester (1.4 g, 4.3 mmol) in dry ether (10 mL) was added a suspension of lithium aluminum hydride (245 mg, 6.5 mmol) in dry ether (40 mL). Stirring at room temperature for 15 1.5 h. The reaction was quenched with water and the product extracted with ether. The combined ether phases were dried $MgSO_4$, filtered and concentrated in vacuo to give 900 mg (91%) of 2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethanol.

c)

20 Under a nitrogen atmosphere, 2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethanol (400 mg, 1.6 mmol), tributylphosphine (480 mg, 2.4 mmol) and 2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (380 mg, 1.6 mmol) were successively dissolved in dry benzene (10 mL). Solid azodicarboxylic dipiperidine (ADDP) (480 mg, 2.4 mmol) was added under stirring at 0 °C to the solution. After 10 min, the reaction mixture was brought to 25 room temperature and the stirring was continued for 16 h. The mixture was added water and the product extracted with ethyl acetate. The combined organic phases was dried ($MgSO_4$), and concentrated in vacuo. The residue was purified chromatography eluting with petroleum ether/ethyl acetate (1:1) to give 300 mg (40%) of the title compound: 1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H), 1.20 (t, 3H), 22.38 (s, 3H), 2.60-2.85 (m, 2H), 2.90-3.05 (m, 3H), 3.25-3.38 (m, 1H), 3.52-3.65 (m, 1H), 3.65-3.75 (m, 1H), 3.75-3.90 (m, 2H), 3.95 (t, 1H), 4.05 (t, 2H), 4.15 (q, 2H), 5.25 (s, 1H), 6.75 (d, 2H), 7.10 (d, 2H), 7.13-7.30 (m, 4H).

EXAMPLE 8

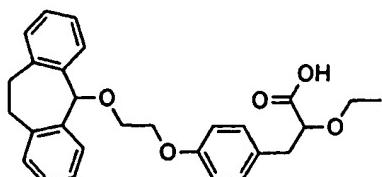
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3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester

10

A mixture of 5-(3-mesyloxypropylidene)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten (5.0 g, 15.2 mmol), ethyl 3-(4-hydroxyphenyl)-2-ethoxypropanoate (3.7 g, 15.5 mmol), potassium carbonate (2.9 g, 21 mmol) and dimethylformamide (10 ml) was heated at 100 °C for 5 h.

Benzene (200 ml) and water (200 ml) were added and the phases were separated. The organic phase was dried and the solvent evaporated in vacuo. The residue was purified by chromatography on silica gel eluting with benzene/chloroform, to give first 2.5 g of 5-propenylidene-10,11-dihydro-5H-dibenzo(a,d)cyclohepten and then 1.5 g (21%) of the title compound as an oil. ¹H NMR (250 MHz, CDCl₃) δ 7.10-7.35 (m, 10 H); 6.85 (d, 2 H); 6.06 (t, 1 H); 4.27 (q, 2 H); 4.07 (m, 3 H); 3.68 (m, 1 H); 3.45 (m, 1 H); 3.17 (bs, 4 H); 3.06 (d, 2 H); 2.69 (q, 2 H); 1.27 (t, 3 H); 0.99 (t, 3 H).

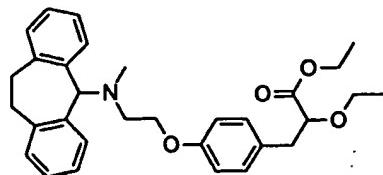
EXAMPLE 9

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3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid

5 3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-
propanoic acid ethyl ester (example 8) (1.5 g, 3.2 mmol) was dissolved in ethanol (30 ml)
and 20% sodium hydroxide (3 ml) was added. After 3 days ethanol was evaporated in
vacuo, water (50 ml) and hydrochloric acid (2 ml) were added and the mixture was extracted
with dichloromethane. The organic phase was dried (MgSO_4) and the solvent evaporated in
10 vacuo. The residue (1.1 g, 78 %) was dissolved in ethanol and treated with (L)-lysine mono-
hydrate (0.41 g). Ethanol was evaporated and the residue triturated with diethyl ether. The
crystalline product was filtered off and dried in the air. This afforded 1.45 g of the title com-
pound as salt with (L)-lysine (dihydrate). M.p. 148-150 °C. ^1H NMR (250 MHz, $\text{DMSO-d}_6\delta$
7.00-7.35 (m, 10 H); 6.75 (bd, $J=8.2$ Hz, 2 H); 6.26 (bs, 8 H); 5.91 (t, $J=6.6$ Hz, 1 H); 4.02 (t,
15 $J=6.2$ Hz, 2 H); 3.76 (m, 1 H); 3.59 (m) + 3.31 (m), 2 H; 3.07 (bs (4 H); 2.70-2.95 (m, 4 H);
2.51 (bq, 2 H); 1.66 (bm, 6 H); 1.03 (t, $J=7.2$ Hz, 3 H).

EXAMPLE 10



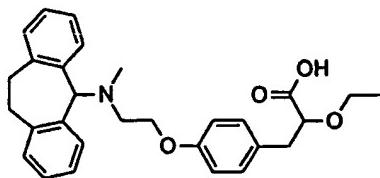
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3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester

25 A mixture of 5-(methylamino)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene hydrochloride (1.8 g, 6.94 mmol), ethyl 3-(4-bromomethoxyphenyl)-2-ethoxypropanoate (2.4 g, 6.95 mmol), potassium carbonate (2.9 g, 21 mmol) and dimethylformamide (7 ml) was heated at 100 °C for 5 h. Benzene (200 ml) and water (200 ml) were added and the phases were separated. The organic phase was dried and the solvent evaporated in vacuo. The residue was purified by

chromatography on silica gel eluting with benzene/chloroform to give 2.2 g (65 %) of the title compound as an oil. RF=0.60 (chloroform/ethanol/ammonia=20:2:0.1)

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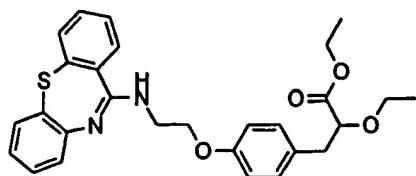
EXAMPLE 11

10 3-(4-[2-((10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid

15 3-(4-[2-((10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester (example 10)(1.5 g, 3.07 mmol) was dissolved in ethanol (20 ml) and 20% sodium hydroxide (2 ml) was added. After 6 days ethanol was evaporated
 in-vacuo, water (50 ml) and acetic acid (2 ml) were added and the mixture was extracted
 with dichloromethane. The organic phase was dried (MgSO_4) and the solvent evaporated in vacuo. The residue (1.4 g) was dissolved in acetone and neutralized with solution of hydrogen chloride in diethyl ether. The solvents were evaporated and the residue was triturated with diethyl ether yielding 1.15 g (74 %) of the title compound as amorphous solid
 20 (hemihydrate). ^1H NMR (250 MHz, $\text{DMSO}-d_6$) δ 10.50 (bs, 1 H); 7.60 (bs) + 7.10-7.50 (m, 10 H), 6.87 (d, $J=7.9$ Hz, 2 H), 5.84 (bd, $J=7.0$ Hz, 1 H), 4.49 (bs, 2 H), 4.00 (t, $J=5.6$ Hz; + bm, 3 H), 3.30-3.60 (m + m, 4 H), 2.80-3.10 (s + bm, 7 H), 1.07 (t, $J=7.2$ Hz, 3 H).

EXAMPLE 12

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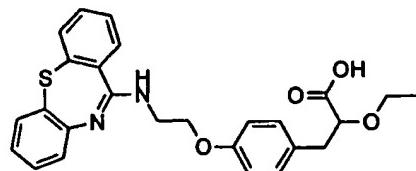
3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester

A mixture of ethyl 3-(4-(2-bromethoxy)phenyl)-2-ethoxypropanoate (3.05 g, 8.8 mmol), potassium phtalimide (2.0 g, 10.8 mmol) and dimethylformamide (20 ml) was heated to 100 °C for 16 h, benzene (200 ml) and water (200 ml) were added and the phases were separated. The organic phase was dried and the solvent evaporated in vacuo. The residue was dissolved in ethanol (60 mL), hydrazine hydrate (1.3 ml) was added and the mixture was refluxed for 2 h, filtered and the solvent evaporated to give 2.4 g (96 %) of ethyl 3-(4-(2-aminoethoxy)phenyl)-2-ethoxypropanoate as an oil. Hydrogen oxalate hemihydrate was prepared for characterization by neutralization with oxalic acid in acetone. M.p. 146-148 °C.

A mixture of dibenzo[b,f]-1,4-thiazepin-11(10H)-thione (2.20 g, 9 mmol; prepared as described in Coll.Czech.Chem.Commun. 48, 1465 (1983), 3-(4-(2-aminoethoxy)phenyl)-2-ethoxypropanoic acid ethyl ester (2.60 g, 8.9 mmol) and 3-methyl-1-butanol (70 ml) was stirred and heated at 150 °C for 16 h. The solvent was evaporated in vacuo, dichloromethane (50 ml) and water (50 ml) were added, the mixture was filtered and the phases were separated. The organic phase was dried (MgSO_4) and the solvent was evaporated in vacuo to give a residue which was purified by column chromatography on silica gel eluting with chloroform. This afforded 0.7 g of the starting thione and then 1.7 g (38 %) of the title compound as an oil. ^1H NMR (250 MHz, CDCl_3) δ 7.05-7.50 (m, 9 H), 6.85-6.95 (m, 3 H), 5.15 (bs, 1 H), 4.25 (m, 2 H), 4.16 (q, $J=7.2$ Hz, 2 H), 3.96 (t + m, 3 H), 3.59 (m, 1 H), 3.34 (m, 1 H), 2.95 (d, $J=6.4$ Hz, 2 H), 1.22 (t, $J=7.2$ Hz, 3 H), 1.16 (t, $J=7.2$ Hz, 3 H).

EXAMPLE 13

25



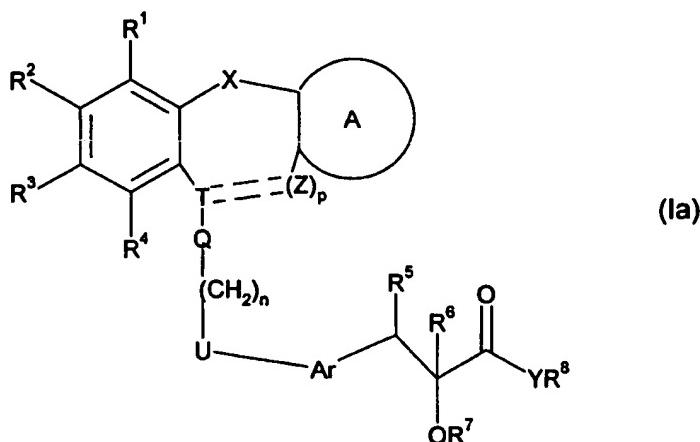
3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid

30 3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester (1.6 g, 3.26 mmol) was dissolved in ethanol (30 ml) and 20% sodium hydroxide (3

ml) was added. After 6 days ethanol was evaporated in vacuo, water (50 ml) and acetic acid (3 ml) were added, the product was filtered off and dried yielding 1.4 g (87 %) of the title compound as hydrate. ^1H NMR (250 MHz, DMSO-d6) δ 7.3-7.6 (m, 6 H), 7.10-7.25 (m, 3 H), 6.82-7.15 (m + bs, 4-5 H), 4.26 (bt, J=4.9 Hz, 2 H), 3.88 (dd, J=7.6 Hz and 4.2 Hz, 1 H), 3.78 (bs, 2 H), 3.54 (m) + 3.25 (m), 2 H; 2.91 (bdd, 1 H), 2.70-2.82 (m, 1 H), 1.03 (t, J=7.2 Hz, 3 H).

Claims:

1. A compound of formula (Ia)



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wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R¹ and R², R² and R³ and/or R³ and R⁴ may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C₁₋₆alkyl;

ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₁₂alkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino,

- aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, halogen, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-, -(NR⁹)-S(O₂)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-(SO₂)-, -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C₁₋₁₂alkyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹³, or -SO₂R¹⁴, wherein R¹³ and R¹⁴ independently of each other are selected from hydroxy, halogen, C₁₋₆alkoxy, amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl;
- T is >N-, >CH-, >C<, -CH₂-N<, Z is -CH₂- , =CH-, >N-, -O-, -S-, >CO, >SO, >SO₂, >NR¹⁵, wherein R¹⁵ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C₁₋₁₂alkyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹⁶, or -SO₂R¹⁷, wherein R¹⁶ and R¹⁷ independently of each other are selected from hydroxy, halogen, C₁₋₆alkoxy, amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl;
- Q is -O-, -S-, >NR¹⁸, wherein R¹⁸ is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C₁₋₁₂alkyl, C₁₋₁₂alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C₁₋₁₂alkyl-amino, arylamino, aralkylamino, aminoC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, aralk-

- oxycarbonyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₁₂alkyl, aralkoxyC₁₋₁₂alkyl, C₁₋₁₂alkylthio, thioC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹⁹, or -SO₂R²⁰, wherein R¹⁹ and R²⁰ independently of each other are selected from hydroxy, halogen, C₁₋₆alkoxy, amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl;
- 5 U is -O-, -S-, >SO₂, >NR²¹, wherein R²¹ is hydrogen or C₁₋₆alkyl,
T==(Z)_p represents a single bond or a double bond,
Ar represents arylene, heteroarylene, or a divalent heterocyclic group optionally substituted with one or more C₁₋₆alkyl or aryl;
- 10 R⁵ represents hydrogen, hydroxy, halogen, C₁₋₁₂alkoxy, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R⁵ forms a bond together with R⁶,
R⁶ represents hydrogen, hydroxy, halogen, C₁₋₁₂alkoxy, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, acyl or aralkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R⁶ forms a bond together with R⁵,
- 15 R⁷ represents hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, C₁₋₁₂alkoxyC₁₋₁₂alkyl, C₁₋₁₂alkoxycarbonyl, aryloxycarbonyl, C₁₋₁₂alkylaminocarbonyl, arylamino-carbonyl, acyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- 20 R⁸ represents hydrogen, C₁₋₁₂alkyl, C₄₋₁₂-alkenynyl, C₂₋₁₂-alkenyl, C₂₋₁₂-alkynyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₁₂alkyl, aryl, hydroxyC₁₋₁₂alkyl or aralkyl groups or when Y is NR¹⁰, R⁸ and R¹⁰ may form a 5 or 6 membered
- 25 nitrogen containing ring, optionally substituted with one or more C₁₋₆alkyl;
n is an integer ranging from 1 to 4,
p is an integer ranging from 0 to 1,
or a pharmaceutically acceptable salt thereof.
- 30 2. A compound according to claim 1 wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxycarbonyl, ary-

- loxy carbonyl, aralkoxy carbonyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;
- 5 or R¹ and R², R² and R³ and/or R³ and R⁴ may form a cyclic ring containing from 5 to 7 carbon atoms optionally substituted with one or more C₁₋₆alkyl.
- 10 3. A compound according to anyone of the preceding claims wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.
- 15 4. A compound according to anyone of the preceding claims wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, C₁₋₇alkyl-amino, arylamino, aralkylamino, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl or C₁₋₇alkylthio.
- 20 5. A compound according to anyone of the preceding claims wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen, perhalomethyl, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, hydroxyC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl or aralkoxyC₁₋₇alkyl.
- 25 6. A compound according to anyone of the preceding claims wherein R¹, R², R³, and R⁴ independently of each other represent hydrogen, halogen or C₁₋₇alkyl.
- 30 7. A compound according to anyone of the preceding claims wherein R¹, R², R³, and R⁴ represent hydrogen.

8. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, 5 heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino, aralkoxycarbonylamino, -COR¹¹, or -SO₂R¹², wherein R¹¹ and R¹² independently of each other are selected from hydroxy, 10 perhalomethyl, C₁₋₆alkoxy or amino optionally substituted with one or more C₁₋₆alkyl, perhalomethyl or aryl; optionally substituted with one or more halogen, perhalomethyl, hydroxy or cyano.

9. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, acylamino, C₁₋₇alkyl-amino, arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl, C₁₋₇alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino, aryloxycarbonylamino or aralkoxycarbonylamino.

10. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, cyano, or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aryloxy, aralkyl, aralkoxy, acyl, hydroxyC₁₋₇alkyl, amino, C₁₋₇alkyl-amino, arylamino, aralkylamino, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl, aralkoxyC₁₋₇alkyl or C₁₋₇alkylthio.

30 11. A compound according to anyone of the preceding claims wherein ring A represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl or C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, C₁₋₇alkoxy, aryl, aralkyl, hydroxyC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₇alkyl, aryloxyC₁₋₇alkyl or aralkoxyC₁₋₇alkyl.

12. A compound according to anyone of the preceding claims wherein ring A represents a 6 membered cyclic ring, optionally substituted with one or more chlorine or methyl groups.

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13. A compound according to anyone of the preceding claims wherein ring A represent a phenyl ring.

14. A compound according to anyone of the preceding claims wherein X is a
10 valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -
(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-
S(O₂)-, -(NR⁹)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-
(SO₂)- or -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, C₁₋₇alkyl, C₁₋₇
alkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocycl, heteroaryl, heteroaralkyl,
15 heteroaryloxy, heteroaralkoxy, hydroxyalkyl, amino, acylamino, C₁₋₇alkyl-amino,
arylamino, aralkylamino, aminoC₁₋₇alkyl, C₁₋₇alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₇alkyl,
aralkoxyC₁₋₇alkyl, C₁₋₁₂alkylthio, thioC₁₋₇alkyl, C₁₋₇alkoxycarbonylamino,
aryloxycarbonylamino or aralkoxycarbonylamino.

20 15. A compound according to anyone of the preceding claims wherein X is a
valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -
(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-
S(O₂)-, -(NR⁹)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-
(SO₂)- or -CH₂-O-CH₂- , wherein R⁹ is hydrogen, halogen, hydroxy, C₁₋₇alkyl, aryl,
25 aralkyl, C₁₋₇alkoxyC₁₋₁₂alkyl, aryloxyC₁₋₇alkyl or aralkoxyC₁₋₇alkyl.

16. A compound according to anyone of the preceding claims wherein X is a
valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -
(NR⁹)-CH₂- , -(CHR⁹)-CH=CH-, -(CHR⁹)-CH₂-CH₂- , -(C=O)-, -O-CH₂-O-, -(NR⁹)-
S(O₂)-, -(NR⁹)-, -CH=(CR⁹)-, -(CO)-(CHR⁹)-, -CH₂-(SO)-, -S-, -(SO)-, -(SO₂)-, -CH₂-
(SO₂)- or -CH₂-O-CH₂- , wherein R⁹ is hydrogen.

17. A compound according to anyone of the preceding claims wherein X is a
valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -
(NR⁹)-CH₂- , -O-CH₂-O-, -(NR⁹)-, -S-, -(SO)- or -CH₂-O-CH₂- , wherein R⁹ is hydrogen.

18. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -(NR⁹)-CH₂- , -O-CH₂-O-, -(NR⁹)-, -S- or -CH₂-O-CH₂- , wherein R⁹ is hydrogen.

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19. A compound according to anyone of the preceding claims wherein X is a valence bond, -(CHR⁹)-, -(CHR⁹)-CH₂- , -CH=CH-, -O-, -O-(CHR⁹)-, -S-(CHR⁹)-, -O-CH₂-O- or -S-, wherein R⁹ is hydrogen.

10 20. A compound according to anyone of the preceding claims wherein X is -S-.

21. A compound according to anyone of the preceding claims wherein T is >C<.

22. A compound according to anyone of the preceding claims wherein Z is -CH₂-, =CH-, >N-, -

15 O-, -S-, >CO, >SO, >SO₂.

23. A compound according to anyone of the preceding claims wherein Z is >N-.

24. A compound according to anyone of the preceding claims wherein Q is -O-, -S-, >NR¹⁸,

20 wherein R¹⁸ is hydrogen or C₁₋₇alkyl.

25. A compound according to anyone of the preceding claims wherein Q is >NR¹⁸, wherein R¹⁸ is hydrogen.

25 26. A compound according to anyone of the preceding claims wherein U is -O-.

27. A compound according to anyone of the preceding claims wherein T==(Z), represents a double bond.

30 28. A compound according to anyone of the preceding claims wherein Ar represents arylene optionally substituted with one or more C₁₋₆alkyl or aryl.

29. A compound according to anyone of the preceding claims wherein Ar represents phenyl.

30. A compound according to anyone of the preceding claims wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₇alkoxy, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl or aralkyl, or R⁵ forms a bond together with R⁶.
- 5 31. A compound according to anyone of the preceding claims wherein R⁵ represents hydrogen or R⁵ forms a bond together with R⁶.
- 10 32. A compound according to anyone of the preceding claims wherein R⁵ represents hydrogen, hydroxy, halogen, C₁₋₇alkoxy, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl or aralkyl, or R⁵ forms a bond together with R⁶.
- 15 33. A compound according to anyone of the preceding claims wherein R⁵ represents hydrogen or R⁵ forms a bond together with R⁶.
- 20 34. A compound according to anyone of the preceding claims wherein R⁷ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, C₁₋₇alkoxyC₁₋₇alkyl, C₁₋₇alkoxycarbonyl, aryloxycarbonyl, C₁₋₇alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocycl, heteroaryl or heteroaralkyl groups.
-
- 25 35. A compound according to anyone of the preceding claims wherein R⁷ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl or C₂₋₇-alkynyl.
- 30 36. A compound according to anyone of the preceding claims wherein R⁷ represents C₁₋₂alkyl.
37. A compound according to anyone of the preceding claims wherein R⁸ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl, aralkyl, heterocycl, heteroaryl or heteroaralkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano.
38. A compound according to anyone of the preceding claims wherein R⁸ represents hydrogen, C₁₋₇alkyl, C₄₋₇-alkenynyl, C₂₋₇-alkenyl, C₂₋₇-alkynyl, aryl or aralkyl.
39. A compound according to anyone of the preceding claims wherein R⁸ represents hydrogen or C₁₋₂alkyl.

40. A compound according to anyone of the preceding claims wherein Y represents oxygen, sulphur or NR¹⁰, where R¹⁰ represents hydrogen, C₁₋₇alkyl, aryl, hydroxyC₁₋₇alkyl or aralkyl groups.

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41. A compound according to anyone of the preceding claims wherein Y represents oxygen.

42. A compound according to anyone of the preceding claims wherein n is an integer ranging from 2 to 3.

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43. A compound according to anyone of the preceding claims wherein p is 1.

44. A compound according to anyone of the preceding claims wherein A is benzo.

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45. A compound according to anyone of the preceding claims wherein X is -O-.

46. A compound according to anyone of the preceding claims wherein X is -S-.

47. A compound according to anyone of the preceding claims wherein Z is -S- and p is 1.

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48. A compound according to anyone of the preceding claims wherein Z is -CH₂- and p is 1.

49. A compound according to anyone of the preceding claims wherein X is =CH- and p is 1.

25

50. A compound according to anyone of the preceding claims wherein T==(Z)_p represents a single bond or a double bond.

51. A compound according to anyone of the preceding claims wherein T is >CH-.

30

52. A compound according to anyone of the preceding claims wherein T is >C<.

53. A compound according to anyone of the preceding claims wherein Q is -O-.

54. A compound according to anyone of the preceding claims wherein Q is -S-.

55. A compound according to anyone of the preceding claims wherein Q is >NR¹⁸, wherein R¹⁸ is H.
- 5 56. A compound according to anyone of the preceding claims wherein n is 2.
57. A compound according to anyone of the preceding claims wherein U is -O-.
58. A compound according to anyone of the preceding claims wherein Ar is phenylene.
- 10 59. A compound according to anyone of the preceding claims wherein R⁵ is H.
60. A compound according to anyone of the preceding claims wherein R⁶ is H.
- 15 61. A compound according to anyone of the preceding claims wherein R⁷ is ethyl.
62. A compound according to anyone of the preceding claims wherein R⁸ is H.
-
63. A compound according to anyone of the preceding claims wherein p is 0.
- 20 64. A compound according to anyone of the preceding claims A is a five membered ring containing S.
65. A compound according to anyone of the preceding claims wherein X is -(CHR⁹)-CH₂-, wherein R⁹ is H.
- 25 66. A compound according to anyone of the preceding claims wherein X is -O-(CHR⁹)-, wherein R⁹ is H.
- 30 67. A compound according to anyone of the preceding claims wherein X is -S-(CHR⁹)-, wherein R⁹ is H.
68. A compound according to anyone of the preceding claims wherein X is -O-CH₂-O-.

69. The compound according to claim 1 which is:

2-Ethoxy-3-{4-[2-(11H-5-oxa-10-thia-dibenzo[a,d]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,

3-(4-[2-(Dibenzo[b,f]-1,4-thiazepin-11-ylamino)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-{4-[2-(Dibenzo[b,f][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-{4-[2-(10,11-Dihydro-dibenzo[b,f]thiepin-10-ylsulfanyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid,

3-(4-[2-[5H-Dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(6,11-Dihydrodibenzo[b,e]thiepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,

3-(4-[2-(6,11-Dihydrodibenzo[b,e]oxepin-11-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid ethyl ester,

3-(4-[2-(2,10-Dichloro-12H-5,7-dioxa-dibenzo[a,d]cycloocten-12-yloxy)-ethoxy]-phenyl)-2-ethoxy-propionic acid,

20 2-Ethoxy-3-(4-[2-(2-methyl-9,10-dihydro-4H-1-oxa-3-aza-benzo[f]azulen-4-yloxy)-ethoxy]-phenyl)-propionic acid ethyl ester,

3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-ethoxy-propanoic acid ethyl ester,

3-(4-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yloxy)-ethoxy]-phenyl)-2-

25 ethoxy-propanoic acid,

3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid ethyl ester,

3-(4-[2-([10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-methyl-amino)-ethoxy]-phenyl)-2-ethoxypropanoic acid;

30 or a pharmaceutically acceptable salt thereof.

70. The compound according to claim 1 which is:

2-Ethoxy-3-{4-[2-(11H-5-oxa-10-thia-dibenzo[a,d]cyclohepten-11-yloxy)-ethoxy]-phenyl}-propionic acid,

3-[4-[2-(Dibenzo[*b,f*][1,4]thiazepin-11-ylamino)-ethoxy]-phenyl]-2-ethoxy-propionic acid,
3-[4-[2-(10,11-Dihydro-dibenzo[*b,f*]thiepin-10-ylsulfanyl)-ethoxy]-phenyl]-2-ethoxy-propionic
acid;
or a pharmaceutically acceptable salt thereof.

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71. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

10 72. A composition according to claim 71 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any-one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

15 73. A pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising, as an active ingredient, a compound according to any-one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

20 74. A pharmaceutical composition useful in the treatment and/or prevention of diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

25 75. A pharmaceutical composition for diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

30 76. A pharmaceutical composition according to any one of the claims 71-75 for oral, nasal, transdermal, pulmonal, or parenteral administration.

77. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding

compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

78. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 71-76.
- 5 79. A method for the treatment and/or prevention of diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to anyone of the preceding claims 71-76.
- 10 80. The method according to claims 77-79, wherein the effective amount of the compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.
-
- 15 81. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.
- 20 82. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).
- 25 83. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.
- 30 84. Use of a compound according to anyone of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and obesity.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 69/734, C07C 59/72, C07D 313/12, C07D 321/12, C07D 337/12,
C07D 281/16, C07D 263/52, A61K 31/185 31/215, 31/335, 31/357, 31/38, A61K 31/554, 31/423,
According to International Patent Classification (IPC) or to both national classification and IPC A61P 3/04, 3/10

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|---|-----------------------|
| P,X | WO 9919313 A1 (DR. REDDY'S RESEARCH FOUNDATION), 22 April 1999 (22.04.99) -- | 1-84 |
| X | STN International, File CAPLUS. CAPLUS accession no. 1998:430714, Document no. 108904, Fukazawa, Nobuyuki et al: "Preparation of hydroxybenzoic acids, their use as cell adhesion inhibitors, and their pharmaceutical compositions", JP,A2,10182550, 19980707 -- | 1-84 |
| X | WO 9604260 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96) -- | 1-84 |

Further documents are listed in the continuation of Box C.

See patent family annex.

- * Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
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- "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

11 February 2000

Date of mailing of the international search report

22 -02- 2000

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/00572

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| X | WO 9604261 A1 (SMITHKLINE BEECHAM PLC), | 1-84 |
| | 15 February 1996 (15.02.96) | |
| | -- | |
| X | WO 9725042 A1 (SMITHKLINE BEECHAM P.L.C.), | 1-84 |
| | 17 July 1997 (17.07.97) | |
| | -- | |
| A | WO 9736579 A1 (GLAXO GROUP LIMITED), | 1-84 |
| | 9 October 1997 (09.10.97) | |
| | -- | |
| | ----- | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **77-80**
because they relate to subject matter not required to be searched by this Authority, namely:
see next page
2. Claims Nos.: **1-84**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The definition of ring A as a 5-6 membered cyclic ring and Ar as arylene, heteroarylene or a heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to compounds that are supported by the examples.

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00572

Claims. 77-80 relate to methods of treatment of the human or animal body by surgery or by therapy./diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

| | |
|-------------------------------|--|
| International application No. | |
| PCT/DK 99/00572 | |

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|--|------------------|--|--|
| WO 9919313 A1 | 22/04/99 | NONE | |
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| WO 9604260 A1 | 15/02/96 | AP 9700918 D AU 697545 B AU 1006199 A AU 3382695 A BG 101180 A BR 9508468 A CA 2196079 A CN 1158123 A CZ 9700254 A EP 0772605 A FI 970357 A GB 9415330 D HU 76637 A IL 114759 D IL 125525 D JP 10503508 T NO 970373 A NZ 292125 A PL 318766 A SK 12297 A TR 960096 A WO 9604261 A GB 9425599 D GB 9509923 D GB 2289999 A | 00/00/00 08/10/98 04/03/99 04/03/96 30/04/98 25/11/97 15/02/96 27/08/97 17/09/97 14/05/97 26/03/97 00/00/00 28/10/97 00/00/00 00/00/00 31/03/98 18/03/97 25/11/98 07/07/97 06/08/97 00/00/00 15/02/96 00/00/00 00/00/00 06/12/95 |
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| WO 9604261 A1 | 15/02/96 | AP 9700918 D AU 697545 B AU 1006199 A AU 3382695 A BG 101180 A BR 9508468 A CA 2196079 A CN 1158123 A CZ 9700254 A EP 0772605 A FI 970357 A GB 9415330 D HU 76637 A IL 114759 D IL 125525 D JP 10503508 T NO 970373 A NZ 292125 A PL 318766 A SK 12297 A TR 960096 A WO 9604260 A GB 9425599 D GB 9509923 D | 00/00/00 08/10/98 04/03/99 04/03/96 30/04/98 25/11/97 15/02/96 27/08/97 17/09/97 14/05/97 26/03/97 00/00/00 28/10/97 00/00/00 00/00/00 31/03/98 18/03/97 25/11/98 07/07/97 06/08/97 00/00/00 15/02/96 00/00/00 00/00/00 |
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INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.

PCT/DK 99/00572

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| WO 9725042 A1 | 17/07/97 | AP 9801272 D AU 1439797 A AU 4839196 A BG 102668 A BR 9706968 A CA 2242632 A CN 1212622 A CZ 9802163 A EP 0815091 A EP 0879053 A GB 9600464 D HU 9900560 A IL 125106 D JP 10511977 T NO 974170 A NO 983147 A PL 327731 A SK 92598 A ZA 9700171 A | 00/00/00 01/08/97 02/10/96 30/04/99 06/04/99 17/07/97 31/03/99 17/02/99 07/01/98 25/11/98 00/00/00 28/07/99 00/00/00 17/11/98 07/11/97 08/09/98 21/12/98 11/01/99 24/07/98 |
| WO 9736579 A1 | 09/10/97 | AU 2506197 A GB 9606805 D | 22/10/97 00/00/00 |

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